

EXHIBIT 1

Fractogel® EMD

Process media

Life Science Products
Processing





Fractogel® EMD Process media

Improves "Process Economics" in the Separation of Bio-Molecules

Specialists in the production of bio-molecules have been using Fractogel® EMD process media for more than 10 years. During the past decade an increasing number of downstream processes have been developed using semi-rigid Fractogel® EMD media in process chromatographic steps.

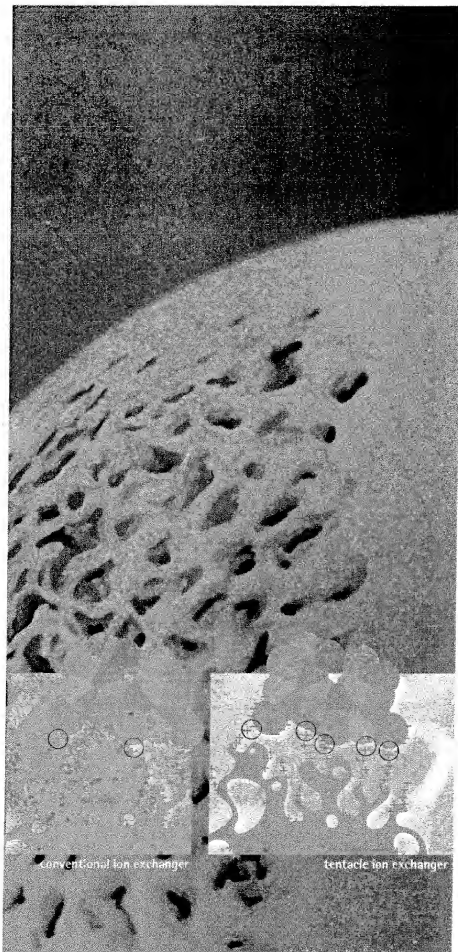
The high efficiency and economy of all Fractogel® EMD media are advantageous due to the strong binding of bio-molecules and the long life time of the material. Above all, Fractogel® EMD process media are used because of the excellent yield together with the high number of cycles over the life time of the product.

High capacity at high flow rates provides a powerful tool for the purification strategy especially if the target molecule is unstable. Saving time not only increases the yield but also improves process economics. Since the binding of bio-molecules is stronger with tentacle exchangers, a higher salt concentration in the sample will affect the binding capacity less compared to conventional gels. So Fractogel® EMD media provide more reliable results, flexibility of use and can be applied successfully to many and varied applications.

Above all, Fractogel® EMD media enables all those involved in Biopharmaceutical processing the use of a well tested production

tool. Compared to conventional resins Fractogel® EMD media improve the efficiency of the separation part of the production process.

Yields are higher, processes can be conducted at higher flow rates therefore reducing throughput time. Because the media lasts so long and can be used repeatedly, the economics of the process are very favourable.



What are Fractogel® EMD process media?

The Matrix

The structure of the Fractogel® particles is considerably different from that of other hydrophilic chromatographic resins like dextran, agarose or cellulose.

Fractogel® is a synthetic methacrylate based polymeric resin providing an excellent pressure stability resulting in high flow rates. The process media consist of beads with a particle size between 40 and 90 µm. Fractogel® EMD

BioSic® for size exclusion chromatography has a particle size in the range of 70-10 µm. The pores which are formed from interwined polymer macromolecules, have a size of about 800 Å enabling a free diffusion of proteins into the beads. The complete surface is strongly hydrophilic due to the ether linkages in the polymer.

The Tentacles

Long, linear polymer chains ("tentacles") carry the functional ligands. All tentacles are covalently attached to hydroxyl groups of the backbone structure of Fractogel®. Thus, both the bead and surface modification are stable to regeneration and sanitization. The main advantage of the tentacle chemistry is the large amount of sterically accessible ligands for the binding of biomolecules without any steric hindrance. Therefore, ligand biomolecules are much more tightly bound during the separation process. Different ligands are utilized for various applications: ion exchange, affinity, hydrophobic interaction chromatography.

Fractogel® EMD media application

Advantages of Fractogel® tentacle media

Better Production Yields

A result of the unique surface modification technique is the high binding capacity of all Fractogel® media. Due to the tighter binding of the target molecule, very often the capture step using Fractogel® ion exchange resins is more efficient than other resins. This more efficient capture results in greater overall yield than with other types of separation media.

Safer Product

In contrast to carbohydrate supports Fractogel® media are resistant to microbial degradation. Thus, the risk of contamination with endotoxins is greatly reduced. In addition the ability to clean Fractogel® media guarantees a long lifetime. This is an important feature especially when recombinant proteins, produced from micro-organisms, are purified.

Very Economical

Due to the chemical resistance of Fractogel® media a high number of cycles can be achieved. Therefore, resin lifetime is extremely long and replacement frequency is minimized resulting in lower operating costs.

Fig. 1:
Capacity at different flow rates.
Only with Fractogel® EMD tentacle
ion exchangers high capacities are
available at high flow rates.

High capacity at high flow rates

High pressure stability

High chemical stability

Strong binding of substances

High recovery of target substances

Freeze stable for distribution

Free of endotoxin, DNase, RNase if used

Regulatory Support Files available

- high throughput

- high flow rates

- easy cleaning in place (CIP)

- efficient capture

- high yield

- good resolution

- high purity of the target molecule

- support for process validation

Matrix crosslinked polymethacrylate

Properties of the tentacle Fractogel® EMD types:

Particle Size S-type: 20 – 40 µm

M-type: 40 – 90 µm

Pore size About 800 Å

pH stability range pH 1 up to 13

Pressure limit 8 bar

Linear flow rate Up to 260 cm/h (S-type),
up to 900 cm/h (M-type)

Storage 150 mM NaCl, 20 % ethanol

Regeneration 1–2 M NaCl for IEX, Citrate, TA,
BioSEC except HIC

Sanitization 0.1 – 0.5 M NaOH

advantage

Application Areas

Rapid protein purification

The main application area of Fractogel® media is the isolation of proteins. Native or recombinant blood plasma factors are processed on Fractogel® EMD ion exchangers with high throughput rates. Peptides and low molecular weight substances (e. g. NADP, ATP, gangliosides) can also be purified efficiently.

Recombinant His-tagged proteins can be purified on Fractogel® EMD Chelate.

Efficient protein polishing

Size exclusion chromatography (SEC) on Fractogel® EMD BioSEC can be used as an efficient polishing step of IgG, IgM, recombinant proteins, plasma factors and others.

High yield antibody isolation

In the case of antibody purification, samples can be loaded directly onto Fractogel® EMD SO₃⁻ (M) and/or Fractogel® EMD SE Hicap whereas serum albumin, nucleic acids, and Phenol Red will not bind. This can remove the need for preparation steps prior to purification. Fractogel® EMD TA is an affinity resin designed specifically for the purification of antibodies and can be utilised instead of ion exchangers or in combination with other methods. The functional group is a small, synthetic ligand, and unlike Protein A, antibodies can be eluted at physiological pH conditions.

Effective DNA removal

DNA removal during the preparation of homogeneous protein samples can be performed using tentacle anion exchange columns, where the DNA binds to the resin. Tentacle cation exchangers can be used to eliminate DNA in the flow-through mode. Small and large scale purification of plasmid DNA is performed on Fractogel® anion exchangers.

Improved virus separation

Fractogel® EMD anion exchangers were shown to be effective in removing a broad range of viruses from process streams. As the binding of virus to the resin was strong, protein could be separated from the contaminating viruses using different salt concentrations. Viral clearance for Fractogel® EMD TMAE and Fractogel® EMD DEAE are in the 5-6 log reduction range. However, it was shown that subsequent elution of virus from these resins in high salt, yielded a large fraction of viable virus enabling the users to calculate the balance of virus reduction. Loading and elution conditions were then investigated that led to the purification of virus on these resins. The use of Fractogel® EMD TMAE or DEAE for the purification of viruses is now replacing the more traditional methods of centrifugation and SEC. Thus, the production of virus particles as well as the removal of viral contamination can be achieved easily using tentacle resins.

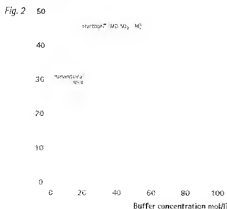
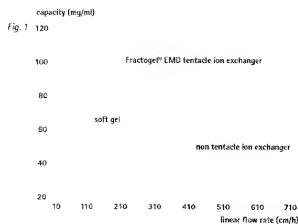


Fig. 2:

Binding of an antibody onto different cation exchangers at pH 6.5. With Fractogel® EMD tentacle ion exchangers high binding capacities can be utilized even at high salt concentrations. The buffer concentration is expressed as the sum of the molarities of sodium chloride and sodium phosphate.

Fractogel® EMD media an excellent

Fig. 3

Reproducibility of 100 cycles on
Fractogel® EMD S03- (M)
The elution positions of the
proteins remain the same for at
least 100 runs

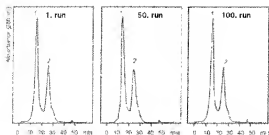
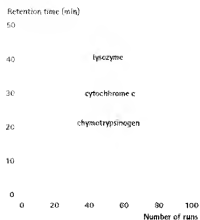


Fig. 4:

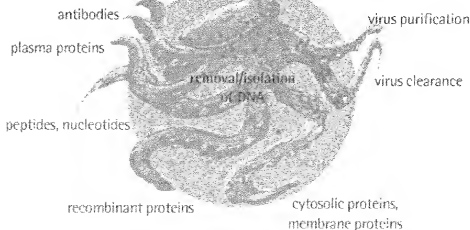
Chromatographic reproducibility
after 100 repetitive injections
onto Fractogel® EMD TMAE (M).
Chromatograms from a
Fractogel® EMD TMAE (M) column
(50-10) showing the separation of
a test mixture containing
conalbumin (peak 1) and human
serum albumin (peak 2).

High Stability – an excellent long term investment

Since the tentacles are very
stable, the resins can be
used for hundreds of cycles.
Even long term treatment
with 0.2 M NaOH for more
than 6 months results in a
loss of binding capacity of
less than 10% of the initial
value. More importantly, no
resin-derived compounds

can be detected in the pro-
tein preparation after the
recommended cleaning
protocols are applied. The
chromatographic perfor-
mance characteristics are
not changed after hundreds
of purification and regen-
eration cycles. Correspond-
ing data are summarised in
the individual Regulatory
Support Files documenta-
tion (RSF).

Application Areas



investment

Fractogel® EMD tentacle media Ordering information

	Description	Catalogue No.	Content EMD	Particle size (µm)	Capacity (µmolarly)	Type of chromatography
Fractogel® IEX media	Fractogel® strong anion exchanger					
	Fractogel® EMD TMAE (M)	1.16051	100, 500, 5000	40-90	100mg BSA	strong anion exchange chromat.
	Fractogel® EMD TMAE (40µm) (M)	1.10276	100, 500, 5000	40-90	100mg BSA	
	Fractogel® EMD TMAE (S)	1.16052	100, 500*	20-40	100mg BSA	
	Fractogel® weak anion exchanger					
	Fractogel® EMD DEAE (M)	1.16058	100, 500, 5000	40-90	100mg BSA	weak anion exchange chromat.
Fractogel® SEC media	Fractogel® EMD DEAE (S)	1.16056	100, 500*	20-40	100mg BSA	
	Fractogel® EMD DEAE (M)	1.16054	100, 500, 5000	40-90	100mg BSA	
	Fractogel® EMD DEAE (S)	1.16050	100, 500*	20-40	100mg BSA	
	Fractogel® strong cation exchanger					
	Fractogel® EMD SO ₃ ⁺ (M)	1.16060	100, 500, 5000	40-90	100mg Lys	strong cation exchange chromat.
	Fractogel® EMD SE-Hrap (M)	1.16064	100, 500, 5000	40-90	100mg Lys	
Fractogel® SEC media	Fractogel® EMD SO ₃ ⁺ (S)	1.16056	100, 500*	20-40	100mg Lys	
	Fractogel® weak cation exchanger					
	Fractogel® EMD COO ⁻ (M)	1.16066	100, 500, 5000	40-90	100mg Lys	weak cation exchange chromat.
	Fractogel® EMD COO ⁻ (S)	1.16062	100, 500*	20-40	100mg Lys	
	Fractogel® EMD BioSep	1.16072	100, 500, 5000	20-40	9-1000 kDa	Size exclusion chromatography
	Fractogel® EMD BioSep	1.16072	100, 500, 5000	20-40	9-1000 kDa	
Fractogel® affinity media	Fractogel® EMD Octylate (M)	1.16078	250, 500, 5000	40-90	80 µmol Cu	metal affinity chromat.
	Fractogel® EMD Amato (M)	1.14893	500, 5000	40-90	40 µmol	affinity chromatography
	Fractogel® EMD TA (S)	1.16073	25, 250	20-40	25mg IgG	chromatographic adsorption
	Fractogel® EMD Eosay (M)	1.16061	100, 1000	40-90	1.5mm ² /g	activated porphyrin immobilisation
	Fractogel® EMD Propyl 650 (S)	1.10068	100, 500*	20-40	25mg Ovalb	weak HIC
	Fractogel® EMD Phenyl 650 (S)	1.14197	100, 500*	20-40	25mg Ovalb	strong HIC

* Larger quantities on request

FDA Registration numbers of Fractogel® media

Product	Cat. No.	250-MF Rev.
Fractogel® EMD TMAE (S, M, 40µm)	1.16051, 1.16052, 1.10276	4140
Fractogel® EMD DEAE (S, M)	1.16056, 1.16058	4004
Fractogel® EMD DEAE (S, M)	1.16050, 1.16054	4752
Fractogel® EMD COO ⁻ (S, M)	1.16062, 1.16066	7133
Fractogel® EMD BioSep (S, M)	1.16072	8114
Fractogel® EMD TMAE (S, M)	1.16051, 1.16052	8095
Fractogel® EMD DEAE (S, M)	1.16056, 1.16058	8229

Selected papers

B.G. Poygren et al., *Endothelin Receptor Receptor Adhesion to Immobilized Endothelin-1 by Column Chromatography*, *Human Gene Therapy* 6:1495-1499 (1995)

C. Pohl et al., *Protein Desorption from the Manufacture of Immobilized FcγR-1*, *Biopharm. J.* 44 (1994) 24-35

M. Gotschalk et al., *Preparedness capturing of mouse monoclonal antibodies from cell culture supernatant by cation exchange chromatography*, *Bio World J.* 3 (1991) 42-44

D. Jovic et al., *Size exclusion chromatography of plasma proteins with high molecular masses*, *J. Chromatogr. A* 706 (1995) 203-206

D. Heilmann et al., *Large scale purification of nucleosides (Nucleoside) and GMP (Nucleoside) by chromatography on Fractogel® High-performance liquid chromatography*, *J. Chromatogr. B* 710 (1998) 1-8

J.K. Walter et al., *Virus Removal and Inactivation*, ACS Symp. Ser. 634: Validation of Biopharmaceutical Processes, Am. Chem. Soc. (1996) 114-124

J.K. Walter et al., *Validation of Virus Safety for Biopharmaceutical Processes*, in: Biopharmaceutical Process Validation, Substantiated by Case Studies, Am. Chem. Soc. (1996) 114-124

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